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First Named Inventor	Shinichi Eda
Art Unit	1641
Examiner Name	G. Gabel
Attorney Docket Number	100554-34635

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ENCLOSURES *(Check all that apply)*

- [x] Fee Transmittal Form
  - [x] Fee Attached
- [ ] Amendment/Reply
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  - [ ] Affidavits/declaration(s)
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1) Petition for a Two Month Extension of Time
2) Return Receipt Postcard

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual name	R. Hain Swope, Esq.; Registration No.: 24,864 Gibbons, Del Deo, Dolan, Griffinger & Vecchione
Signature	R. Hain Swope
Date	June 22, 2004

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

APPLICANT(S)	:	EDA *et al.*	EXAMINER	:	G. Gabel
SERIAL NO.	:	09/827,846	ART UNIT	:	1641
FILED	:	April 6, 2001			
FOR	:	MICROPARTICLE ENHANCED LIGHT SCATTERING AGGLUTINATION ASSAY AND MICROPARTICLE REAGENTS THEREFOR			
ATTORNEY DOCKET	:	100554/34635			

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BRIEF OF APPELLANT

This brief is in furtherance of the Notice of Appeal filed in this case on February 27, 2004. This is an appeal from the Final Rejection of the Examiner dated October 31, 2003 rejecting Claims 1-4, 6, 9, 10, 20, 22 and 23 and the Advisory Action of January 23, 2004. This Brief is submitted in triplicate and is accompanied by the requisite fees set forth in 37 C.F.R. § 1.17(c). A Petition for a Two-Month Extension of Time also accompanies this Brief with the requisite fee set forth in 37 C.F.R. § 1.17(a)(2).

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REAL PARTY IN INTEREST

The real and only party in interest in this application is assignee of record, Roche Diagnostics Corporation, Indianapolis, Indiana

RELATED APPEALS AND INTERFERENCES

None.

STATUS OF CLAIMS

For purposes of Appeal, the status of the claims is (or will be) as follows:

Claims 1-4, 6, 9, 10, 20, 22 and 23 are (or will be) rejected

Claims 5, 7, 8, 11-19 and 21 are (or will be) canceled.

The appealed claims are: 1-4, 6, 9, 10, 20, 22 and 23

STATUS OF AMENDMENTS

Claims 1-17 and 19-21 were finally rejected in the Office Action of June 4, 2002. Appellants' Request for Reconsideration filed September 3, 2002 presenting amended claim 1 and canceling claims 19 and 21 has been or will be entered for purposes of appeal according to the Advisory Action dated September 18, 2002. The Examiner indicated in an Advisory Action mailed September 18, 2002 that the amendment and argument would be entered, but claims 1-17 and 19-21 would continue under rejection. Appellants filed an Appeal on November 1, 2002 and a Brief on Appeal on January 6, 2003. On April 7, 2003, the Examiner reopened prosecution withdrawing the previous grounds of rejection and raising new grounds of rejection under 35

U.S.C. §102 and 35 U.S.C. §103 over Lindmo *et al.*, previously of record. Amendments to Claims 1, 6 and 10 having been entered, Claims 1-4, 6, 9, 10, 20, 22 and 23 were finally rejected in the Final Office Action of October 31, 2003. In answer to Appellants' Amendment in response thereto the amendment to Claim 20 has been or will be entered for purposes of appeal according to the extensive Advisory Action mailed January 23, 2004. The restated rejections and responses to Appellants' arguments in the Advisory Action will be addressed below.

SUMMARY OF THE INVENTION

The present invention provides a reagent for performing a microparticle enhanced light scattering agglutination assay that offers a larger dynamic range than heretofore known. (Specification, page 2, lines 18-21). The assay of the invention can be used for determining an analyte for which there are binding partners apt to be bound to microparticles that specifically recognize the analyte. (Id., page 10, lines 3-6). The assay reagent comprises a binary mixture of two particle types, each having a mean diameter of from 300-600 nm: 1) microparticles of strong light scattering properties carrying at least one binding partner of high reactivity (high affinity) for the analyte, and 2) particles of weak light scattering properties carrying at least one binding partner of low reactivity (low affinity) for the analyte (Id., page 6 lines 20-22, page 7 lines 1-2 and page 19, lines 1-5).

The size and/or the refractive index ratio of the microparticles of Appellants' invention is such that they can cause light scattering at the wavelength used for detection of agglutinated microparticles, typically from 300 nm to 1200 nm. Accordingly, particle size is generally chosen to be substantially smaller or slightly smaller than that wavelength. The particles of strong light

scattering properties preferably have a higher refractive index and/or a larger size than the particles of weak light scattering properties. (Id., page 8, lines 7-9).

The binding partners (e.g. antibodies) of high and low affinity are selected so as to cause an agglutination reaction that is detectable by, for example, turbidimetry or nephelometry (Id., e.g., page 1, lines 8-17; page 4, lines 11-16; page 17, line 17). By using a binary mixture of two particle type populations, the measurements obtained from the high reactivity particles provide high precision in the low concentration range and the measurements of low reactivity particles provide an increase in binding at high concentrations even after the high affinity particles have been saturated, avoiding the well known "hook effect." The assay shows an unexpectedly high dynamic range (DR) (Id., page 7, lines 2-3) for an agglutination assay.

Thus, the reagent of the invention comprises a mixture of microparticles of 30 to 600 nm (preferably from 50 to 500 nm) in diameter, including particles of strong light scattering properties carrying at least one binding partner of high reactivity (affinity) for the analyte and particles of weak light scattering properties carrying at least one binding partner of low reactivity (affinity) for the analyte. (Id., page 19, lines 1-5).

According to one preferred embodiment, the "particles of strong light scattering properties" and the "particles of weak light scattering properties" are microparticles of the same size but made of different materials, the material of the former particles having a substantially higher refractive index than the material of the latter particles. The ratio of the refractive index of the particles of strong light scattering properties to that of the particles of weak light scattering properties is then suitably at least 1.2, preferably at least 1.5. (Id., page 8, lines 10-16).

The particles have a composition selected from the group consisting of selenium, carbon, gold, a nitride of carbon, a nitride of silicium, a nitride of germanium, an oxide of iron, an oxide of titanium, an oxide of silicium, an epoxy resin, polyvinyl chloride, polyvinylidene chloride, polyalpha-naphthylmethacrylate, polvinylnaphthalene, polystyrene and a copolymer thereof (Id. Page 9, lines 10-21).

According to another preferred embodiment, the "particles of strong light scattering properties" and the "particles of weak light scattering properties" are microparticles of the same material but having different sizes, the size of the former particles, referred to as "large particles", being substantially larger than that of the latter, referred to as "small particles". The mean diameter of the large particles is suitably from 160 to 600 nm, preferably from 190 to 500 nm. The ratio between the mean diameter of the large particles and the mean diameter of the small particles is suitably from 1.5 to 4.0, preferably from 1.7 to 3.2 (Id., page 8, lines 17-22 and page 9, lines 1-3). The concentration ratio of the first microparticles to the second microparticles is preferably from about 0.01 to about 5.0 (Id. Page 9, lines 8-9).

In further preferred embodiments, the analyte measured by the reagent of the invention is a nucleic acid and the first and second binding partners are oligonucleotide capture probes (Id. page 10, lines 8-9) or the analyte is antigenic and the first and second binding partners are monoclonal antibodies or fragments thereof (Id. Page 10, lines 7-8, page 14, lines 9-11 and page 15, line 4-8).

In still further preferred embodiments, the analyte measured by the reagent of the invention is a C-reactive protein and the first and second binding partners recognize different epitopes of C-reactive protein (Id. page 10, lines 16-17, page 15, lines 8-11 and Example 2, pages

41-52) or the analyte is prostate specific antigen and the first and second binding partners recognize different epitopes of prostate specific antigen (Id. Page 11, lines 1-2, page 15, lines 8-11 and Example 1, pages 19-40).

ISSUES

Are Claims 1-4, 6, 10 and 20 unpatentable under 35 U.S.C. §103(a) over Lindmo *et al.* (Journal of Immunological Methods, 126: 183-189 (1990)) in view of Grange *et al.*(Journal of Immunological Methods (1977))*?* Is Claim 9 unpatentable under 35 U.S.C. §103(a) over Lindmo *et al.* (Journal of Immunological Methods, 126: 183-189 (1990)) in view of Grange *et al.*(Journal of Immunological Methods (1977)) as applied to Claims 1-4, 6, 10 and 20, further in view of Sutton *et al.* (USP 5,550,891? Is Claim 22 unpatentable under 35 U.S.C. §103(a) over Lindmo *et al.* (Journal of Immunological Methods, 126: 183-189 (1990)) in view of Grange *et al.*(Journal of Immunological Methods (1977)) as applied to Claims 1-4, 6, 10 and 20, further in view of Collet-Cassart *et al.* (USP 4,556,642)? Is Claim 23 unpatentable under 35 U.S.C. §103(a) over Lindmo *et al.* (Journal of Immunological Methods, 126: 183-189 (1990)) in view of Grange *et al.*(Journal of Immunological Methods (1977)) as applied to Claims 1-4, 6, 10 and 20, further in view of Kapmeter *et al.* (Clinical chemistry, (1966) Vol. 42, No. 6 PART 2, pp S268-S269)? Is it proper to reconstruct the claimed microparticle agglutination reagent by modifying the individually distinguishable microparticles of Lindmo *et al.*'s flow cytometry reagents according to the critical functional characteristics, especially particle size, of the indistinguishable microparticles of Grange's agglutination reagents, assuming equivalencies that

are not disclosed, in order to reject the claimed reagent, although none of the citations of record teaches differential characterization between microparticles in agglutination reagents?

GROUPING OF CLAIMS

The claims stand or fall together.

ARGUMENT

The rejection of Claims 1-4, 6, 10 and 20 under 35 U.S.C. § 103(a) as being unpatentable over the teachings of Lindmo *et al.* (Journal of Immunological Methods, 126: 183-189 (1990)) in view of Grange *et al.*(Journal of Immunological Methods (1977)) is improper.

Lindmo *et al.* teach an assay based on flow cytometry, wherein there is no aggregation of microparticles, and wherein the amount of soluble labeled antibody is determined for each particle individually as they are separated and discriminated by a flow cytometer. A calibration curve for each particle with a distinguishing feature is generated. Appellants submit that one skilled in the art would understand that the microparticle reagent produced by Lindmo *et al.* would not share the same structural and functional characteristics as those of the claimed agglutination reagent since the assay of Lindmo *et al.* is based on principles unrelated to those of the claimed reagent. Lindmo *et al*'s reagent requires that, "all particle types must be individually distinguishable, e.g. by size in flow cytometric analysis" (See Lindmo *et al.*, page 188 col. 1). The requirement in Lindmo *et al.*, that the particle types be individually distinguishable by flow cytometry excludes the claimed microparticles which are capable of causing light scattering at wavelengths suitable for the detection of agglutinated microparticles, and are inherently not individually distinguishable by flow cytometry. Regarding techniques

based on individual particle counting such as flow cytometry versus techniques based on agglutination, such as nephelometry and turbidimetry, "direct comparison is often difficult because different particle sizes are appropriate for different detection systems..." (Newman et al., page 37 col. 1, Citation of Record).

Lindmo *et al.* does disclose a reagent incorporating a binary mixture of microparticles utilized in an assay based on differential reactivity and dissociation constants between two immunological binding partners in flow cytometry applications. However, there is neither teaching nor suggestion therein of an assay based on agglutination applications. It is submitted that, in spite of the fact that the particles disclosed by Lindmo *et al.* possess characteristics seemingly in parallel to those of the claimed invention, they differ appreciably in size and it is that difference that distinguishes the principles upon which the assays of Lindmo *et al.* and Appellants are based. This distinction is critical because particles suitable for use in one of these assays are not suitable for use in the other and vice versa.

The particles taught by Lindmo *et al.*. are not colloidal, but are "relatively large" (See Lindmo *et al.*, page 184, column 2), i.e. 7-10 μm in diameter, which renders them individually distinguishable by flow cytometry, but also renders them incapable of producing meaningful results in an agglutination assay as taught by Appellants. It is clear that, unlike the particles described by Lindmo *et al.*, the microparticles of Appellants' reagent are colloidal particles of a defined particle size range that are suitable for agglutination assays. This size range (30 to 600 nm) renders the particles of Appellants' reagent structurally capable of causing light scattering at wave lengths used for detection in agglutination assays. Since the assay of Lindmo *et al.* is based on principles unrelated to those for which the claimed reagent is suitable, the person of

ordinary skill in the art would understand that the flow cytometry reagent disclosed in Lindmo *et al.* does not share the structural and functional characteristics of Appellants' reagent. The Examiner has tacitly admitted as much when she withdrew the anticipation rejection over Lindmo *et al.* under 35 U.S.C. § 102 earlier in the prosecution.

In an effort to correct the deficiencies of Lindmo *et al.*, the Examiner has cited Grange *et al.*, but only as a teaching of a particle size range suitable for detection in an agglutination assa, i.e. about 300 nm. This is undoubtedly because Grange *et al.*, which at one point in the prosecution was the primary citation, and at another point, was completely withdrawn, fails to teach differential characterization between two microparticle populations and fails to teach differential reactivity and dissociation constants between two immunological binding partners. The Examiner asserts that it would be obvious to generate microparticles in the size range of about 300 nm and incorporate them in the assay of Lindmo *et al.* Appellants contend that there is neither reason nor motivation for doing so because microparticles of 300 nm are not suitable for the assay taught by Lindmo *et al.* that is based on different principles than an assay requiring particles in that size range.

THE REJECTIONS UNDER 35 U.S.C. 103 (a) ARE IMPROPER BECAUSE THERE IS NO TEACHING OR SUGGESTION TO COMBINE THE CITATIONS

MPEP 706.02(j) states that in order for the claims of the instant Application to be obvious in light of the teachings of the cited references:

> ...three basic criteria must be met.
>
> First, there must be some suggestion or motivation, either in the [reference itself], or in the knowledge generally available to one of ordinary skill in the art, to modify the reference....

Second, there must be a reasonable expectation of success.

Finally, the prior art reference (or references combined) must teach or suggest all the claimed limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art. (MPEP 706.02(j)).

A. THERE IS NO MOTIVATION TO MODIFY LINDMO *ET AL.*

The Examiner takes the position that it would have been obvious for one of ordinary skill in the art to generate particles in the size range of about 300 nm as taught by Grange *et al.* for incorporation into the reagent taught by Lindmo *et al.* for use in agglutination assay detection methods because Grange *et al.* specifically teach that intensity of light scatter by a given suspension of microparticles in a reagent, when used in an agglutination assay, is dependent of the size and number of the particles. First of all, this statement is not consistent with the Examiner's assertion that Grange *et al.* is replied upon only for a disclosure of a particular particle size. Regardless, the key portion of the statement is "when used in an agglutination assay". Lindmo *et al.* does not teach an agglutination assay. Lindmo *et al.* teaches an assay that is based on principles clearly distinct from an agglutination assay utilizing particles of a size such that they would not be suitable for an agglutination assay. Therefore, there is no reason why one of ordinary skill in the art would want to add particles clearly unsuited for the assay described by Lindmo et al. to their reagent.

Lindmo *et al.* teaches an assay based on flow cytometry, wherein there is no agglutination of microparticles, that requires an assay reagent with particles of a relatively large size (7-10 μm in diameter) which can be individually distinguished in a flow cytometer. The statement by the

Examiner that particles in the size range of about 300 nm might be incorporated into the reagent taught by Lindmo *et al.* for use in agglutination assay completely overlooks the fact that there is no reason given in the record why the skilled artisan would attempt to utilize the particles taught by Lindmo *et al.* in an agglutination assay, for which they are clearly unsuited. Therefore, there is neither reason nor motivation to add particles to the Lindmo *et al.* reagent that would be clearly unsuitable for the stated assay. There is further neither reason nor motivation therein to add particles foreign to the stated assay with the expectation of carrying out a different assay for which the Lindmo *et al.* particles are unsuitable.

B. THERE CAN BE NO REASONABLE EXPECTATION OF SUCCESS

It is Appellants' contention that the particles taught by Lindmo *et al.* are not suitable for an agglutination assay and diluting them with much finer microparticles of the size taught by Grange *et al.* will neither make them suitable for such an assay, nor improve them for their original intended use. The continued addition of such fine microparticles to the particles of Lindmo *et al.* would eventually be detrimental to the purpose of the assay taught by Lindmo *et al.* which is based on the principles of flow cytometry wherein the particles must remain monodispersed so that they can be individually detected by a flow cytometer. The person of ordinary skill in the art would understand that the flow cytometry reagent disclosed in Lindmo *et al.* does not share the structural and functional characteristics of the claimed agglutination assay reagent and would not by utilized by chance or design in an agglutination assay. Therefore, it is Appellants' contention that a reasonable expectation of success has neither been established on the record, nor can it in any way be inferred from the teachings of Lindmo *et al.* The Examiner's

position that one of ordinary skill in the art would add particles of 300 nm to a reagent as taught by Lindmo *et al.* is submitted to be based on an impermissible hindsight construction rather than an assertion of a reasonable likelihood of success, which cannot be sustained in any event.

Appellants arrived at the claimed invention as a whole through targeted research and development well beyond that which would be obvious to one of ordinary skill in view of the citations of record. With the unpredictability taught by the art, clearly there is no expectation of success provided by Lindmo *et al.* in view of Grange *et al.* Without such an expectation in the art, the disclosure that certain reagents exist which contain larger and smaller particles that have light scattering properties that can be distinguished in a flow cytometer makes it, at best, obvious to try. Patentability considerations based on an obvious to try logic are contrary to 35 U.S.C. §103(a) because that logic disregards consideration of the "invention as a whole" concept of 35 U.S.C. 103. In re Tomlinson, 363 F2d 928, 150 USPQ 623 (CCPA 1966 and In re Dien 371 F. 2d 866, 152 USPQ 550 (CCPA 1967).

C. THERE IS NO MOTIVATION IN THE CITATIONS RELIED UPON THEMSELVES TO COMBINE THE TEACHINGS OF LINDMO *ET AL.* AND GRANGE *ET AL.* IN A MANNER WHICH RENDERS THE CLAIMED SUBJECT MATTER OBVIOUS BECAUSE THEY TEACH AWAY FROM ONE ANOTHER

Lindmo *et al.* discloses differential characterization between two microparticle populations, differential reactivity and dissociation constants between two immunological binding partners in flow cytometry applications, however it does not teach or suggest agglutination applications. Further, the particles taught by *Lindmo et al.*. are not colloidal, but are "relatively large" (See *Lindmo et al.*, page 184, column 2), i.e. 7-10 μm in diameter, which

renders them individually distinguishable by flow cytometry, but also renders them incapable of producing meaningful results in an agglutination assay. Grange *et al.* discloses the use of a specific particle type in agglutination assay applications but, by the Examiner's own admission, Grange *et al.* differs from the present invention in "failing to teach differential characterization between two microparticle populations. Grange *et al.* also fails to teach differential reactivity and dissociation constants between two immunological binding partners" (See Office Action of June 4, 2002, Page 4, lines 6-8).

While Grange *et al.* is only relied upon for a disclosure of light scattering microparticles having a diameter of 300 nm for measurement at wavelengths of 220 nm to 600 nm, that teaching cannot be lifted out of the context of the citation and combined with Lindmo *et al.* with which it is incompatible as a practical matter, other than by a hindsight construction based on Appellants' disclosure. The Examiner cannot rely on hindsight to arrive at a determination of obviousness, *In re Fritch*, 23 U.S.P.Q.2d 1780, 1784 (Fed. Cir. 1992). The Court of Appeals for the Federal Circuit has stated that "selective hindsight is no more applicable to the design of experiments than it is to the combination of prior art teachings. There must be a reason or suggestion in the art for selecting the procedure used, ***other than the knowledge learned from the Appellants' disclosure*** (emphasis added)." [*Interconnect Planning Corporation v. Fed.*, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985)]. *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988).

It is Appellants' position that there is nothing in the teachings of Lindmo *et al.* that would in any way suggest to the person skilled in the art the addition to the reagent disclosed therein of particles that are not suited for the stated assay. There is no teaching in Lindmo et al. that would in any way suggest the use of the particles disclosed therein in any other type of assay, with or

without the addition of particles undefined and undisclosed therein. There is nothing in the teaching of Grange *et al.* of light scattering microparticles having a diameter of 300 nm for measurement at wavelengths of 220 nm to 600 nm that would suggest that such particles would be useful in an assay based on the principles of flow cytometry, which require that particle types in the assay be individually distinguishable, i.e. they do not agglutinate (see the discussion in Lindmo *et a.l*, page 188, col. 1 3rd full paragraph, which clearly teaches away from the use of particles that agglutinate).

The Examiner states in the Advisory Action mailed January 23, 2004 that, if the prior art structure created by the combined teaching of Lindmo *et al.* and Grange *et al.* is capable of performing the intended use, then it meets the claim. It is respectfully submitted that this statement begs the question, and incorrectly assumes that the two citations are combinable. Merely mixing applications and materials does not elevate the disclosure into a teaching or suggestion to combine Grange *et al.* and Lindmo *et al.* "The range of sources available ... does not diminish the requirement for actual evidence. That is, the showing must be clear and particular" *In re Dembiczak* , 50 U.S.P.Q. at 1617. The case law calls for a "rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references." *Id. See also, C.R. Bard, Inc. v. M3 Sys., Inc.*, 48 U.S.P.Q. 2d 1225, 1232 (1998), (describing "teaching or suggestion or motivation [to combine]" as an "essential evidentiary component of an obviousness holding".) Appellants have argued that, because particles such as those disclosed by Grange *et al.* are unsuited for the assay taught by Lindmo *et al.*, the addition thereof would not only lack any beneficial effect, but due to their inherent tendency to agglutinate, would adversely

impact the efficacy of the Lindmo *et al.* assay in view of the requirement that all particle types in the assay be individually distinguishable.

D. THE EXAMINER HAS OFFERED NO PARTICULAR FACTUAL SHOWING REGARDING THE LOCUS OF THE SUGGESTION, TEACHING OR MOTIVATION TO COMBINE LINDMO *ET AL.* AND GRANGE *ET AL.*

The Examiner has emphasized the aspects of the reagent taught by Lindmo *et al.* that are similar to Appellants' reagent, i.e. a binary mixture of microparticles having two distinguishable types, coated with binding partners having the same specificity but different reactivity and the like. However, the Examiner has not proffered a particular factual showing regarding the locus of the suggestion, teaching or motivation to combine Lindmo *et al.* with the disclosure of particles of a particular size and light scattering capacity as taught by Grange et al. to arrive at the reagent of the Claims on Appeal. Instead, the Examiner argues that Appellants cannot establish nonobviousness by attacking the references individually when the rejection is based on the combination. The Examiner replies on In re Keller, 208 USPQ 871 (C.C.P.A. 1981) and In re Merck & Co., 231 USPQ 375 (Fed. Cir. 1986). Neither meets the facts of this Appeal

In Keller, the claimed invention was a pacemaker incorporating a digital timer. The rejections were A in view of C and B in view of C, wherein both A and B disclosed pacemakers incorporating analog timers and C was a general article describing the advantages of digital timers over analog timers. The applicant attacked citation C on the grounds that it did not mention pacemakers in any context. In Merck, the claimed compound and the prior art compound differed only in the presence of a nitrogen and an unsaturated carbon, respectively, in one ring of their chemical structures. There was a citation of record that was a general review

article discussing the relationships of chemical structures and which contained no reference to the prior art compound. The review article suggested that, in molecules possessing pharmaceutical activity having at least one ring in their chemical structures, a nitrogen and an unsaturated carbon atom in such rings were bioisosteric, and therefore interchangeable. The essence of the ruling was that the citation teaching the bioisosteric pathways could not be viewed in a vacuum and had to be taken in the context of the prior art compound, which had similar activity to the claimed compound. It is noted that the dissent argued that the teaching of the bioisosteric pathways citation amounted to no more than an invitation to experiment.

Both of these decisions involve a generalized secondary citation that was used in combination with a primary citation to focus it on the claimed invention, in both instances, the secondary citation was not particularly relevant to the claims under consideration taken by itself. The Court admonished the Appellants against attacking the secondary reference on the basis of what it didn't teach, instead of focusing on the combination of its teachings with the primary citation. Such is not the case in this Appeal. The rejection here is based on the combination of two citations, Lindmo *et al.* and Grange *et al.*, there is no general teaching of the type of record in Keller and Merck. Therefore, the Examiner's reliance of these decision is misplaced. Appellants are entitled to attack the combination Lindmo *et al.* and Grange *et al.* by showing that there is no basis in either citation for combining them, that is not tantamount to an attack on the citations individually. In fact, the portion of Merck that cautions against taking any citation in a vacuum, as is being done here with the particle size statement in Grange *et al.*, would appear to be most germane to the present Appeal.

It is Appellants' position that the locus of the basis for combining Lindmo *et al.* and Grange *et al.* has not been satisfactorily established in the record. It is further Appellants' contention that, in fact, the two citations represent a difference in principle such that a portion of either cannot be lifted out of context and combined with the other, both because the exercise of impermissible hindsight would be required and the fact that they are simply not compatible teachings. The obvious difficulty experienced by the Examiner in attempting to combine these citations is further evidenced by the fact that, during the course of prosecution of the above-identified patent application, the Claims have been rejected as being unpatentable over Grange *et al.* in view of Lindmo *et al.*,(reference the first Brief on Appeal filed January 6, 2003), as anticipated by Lindmo *et al.* and now as unpatentable over Lindmo *et al.* in view of Grange *et al.*

The rejection of Claim 9 under 35 U.S.C. §103(a) as being unpatentable over Lindmo *et al.* in view of Grange *et al.*, further in view of Sutton *et al.* (USP 5,330,891) is improper. The arguments noted above with respect to the Examiner's assertion that Appellants are attacking the citations rather than the combination are equally applicable in this instance and will not be repeated for brevity. Based only on the fact that Sutton *et al.* teaches the use of oligonucleotide capture probes for a nucleic acid analyte, which is known in the art, it is respectfully submitted that one of ordinary skill in the art would not be led to create the reagent of Claim 9 by combining the teachings of Sutton *et al.* with Grange *et al.* and certainly not by combining the teachings of Sutton *et al.* with Lindmo *et al.*. It is stated in the Advisory that it would be obvious to covalently attach oligonucleotide probes, such as taught by Sutton *et al.*, into the reagent taught by Lindmo *et al.* as modified, it is assumed by size reduction, as taught by Grange *et al.* This would envisage an even further departure from the teachings of Lindmo *et al.* whose

microparticles have antibody adsorbed on their surfaces as opposed to being covalently bonded. In addition to being devoid of a teaching or suggestion that the size of their particles should be reduced to a point where they would no longer be suitable for the intended assay, there is neither teaching no suggestion in Lindmo *et al.* that any probe or similar molecular entity be covalently bonded to the disclosed particles.

The rejection of Claim 22 under 35 U.S.C. §103(a) as being unpatentable over Lindmo *et al.* in view of Grange *et al.* further in view of Collet-Cassart *et al.* (USP 4,556,642) is improper. The arguments noted above with respect to the Examiner's assertion that Appellants are attacking the citations rather than the combination are equally applicable in this instance and will not be repeated for brevity. Appellants continue to take issue with the conclusionary and unsupported statement by the Examiner in the Final Office Action that the combination of Lindmo *et al.* and Grange *et al.* differ from the invention as claimed in Claim 22 only in failing to teach that the analyte tested for is C-reactive (CRP) protein and that the immunological binding partners recognize different epitopes of the CRP protein. Collet-Cassart disclose an agglutination reaction which, as discussed throughout this Brief, is a major distinction and departure from the assay disclosed by Lindmo *et al.* Further, the reaction taught by Collet-Cassart is, in principle, a methodology based on a single particle type whereby the results are obtained by varying concentrations in a competitive binding situation. This is a departure from both Lindmo *et al.* and Grange *et al.* as well as Appellant's claimed reagent. There is absolutely no roadmap available in the citations of record, other than Appellants' disclosure that would lead one of ordinary skill in the art to make the multiple major modifications of the reagent taught by Lindmo et al. to arrive at the reagent of Claim 22.

The rejection of Claim 23 under 35 U.S.C. §103(a) as being unpatentable over Lindmo *et al.* in view of Grange *et al.* further in view of Kapmeter *et al.* (Clinical chemistry, (1966) Vol. 42, No. 6 PART 2, pp S268-S269) is improper. The arguments noted above with respect to the Examiner's assertion that Appellants are attacking the citations rather than the combination are equally applicable in this instance and will not be repeated for brevity. Kapmeyer *et al.* teach that PSA is an important analyte and disclose that they have developed a test therefore based on light scattering. However, there is nothing to suggest to one of ordinary skill in the art a diagnostic test comprising Applicants' novel reagent having PSA as the analyte, since Applicants' reagent is neither taught nor suggested by Lindmo *et al.* and Grange *et al.*. The Examiner admits in the Advisory Action that Kapmeyer *et al.* teach an agglutination assay. The large particles of Lindmo *et al.* are totally unsuited for an agglutination assay, regardless of the nature of the analyte. As is clear from the foregoing arguments, Lindmo *et al.* and Grange *et al.* are not combinable and, in fact, teach away from each other. The incorporation of a particular analyte does not change this, particularly when it is considered that it is lifted from the context of an agglutination assay, in principle clearly distinguished from the teaching of Lindmo *et al.* Thus, due to the great disparity between Appellants' Invention and the teachings of these citations, it is respectfully submitted that one of ordinary skill in the art would ***never*** be motivated to combine their teachings as the Examiner has done in making the rejections. Rather, ***Appellants' disclosure*** has provided motivation for the Examiner's attempt to combine these citations. Appellants submit that a reagent and its properties cannot be separated for purposes of making a rejection when the properties thereof are inherent. Moreover, when a property, specifically the utility of the reagent, is the fundamental distinction between the reagents of the

citations, there can be no suggestion that they be combined to arrive at the reagent of the Claims on consideration in this Appeal. Absent a teaching or suggestion in the record that would motivate one of ordinary skill in the art to combine the citations as the Examiner as attempted to do in making the rejections, they are not properly combinable.

A PRIMA FACIE CASE OF OBVIOUSNESS HAS NOT BEEN ESTABLISHED

The Examiner bears the burden of establishing a prima facie case of obviousness based upon the citations of record. (See *In re Fritch*, 23 USPQ 2d 1780, 1783 (Fed. Cir. 1992), *In re Oetiker*, 24 USPQ 2d 1443, 1446 (Fed. Cir. 1992), and *In re Deuel*, 34 USPQ 2d 1210, 1214 (Fed. Cir. 1995)). The Court has held that:

> The examiner bears the burden of establishing a prima facie case of obviousness. . . . Only if this burden is met does the burden of coming forward with rebuttal argument or evidence shift to the applicant. . . . When the references cited by the examiner fail to establish a prima facie case of obviousness, the rejection is improper and will be overturned. *In re Deuel*, 34 USPQ 2d 1210, 1214 (Fed. Cir. 1995)
>
> A prima facie case of obviousness is not established unless the relied-upon references contain some "teaching, suggestion, or incentive" supporting the combination. *In re Geiger*, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987).

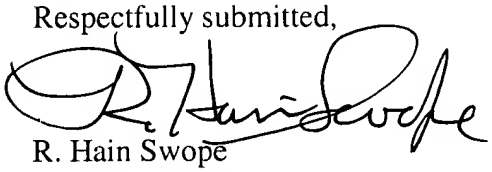
It is respectfully submitted that there is no nexus in the record by which one of ordinary skill in the art would combine the teachings of Lindmo *et al* and Grange *et al* other than Appellants' disclosure. A prima facie case of obviousness not been established.

CONCLUSION

Appellants respectfully submit that there is no teaching, suggestion or motivation for combining the teachings of Lindmo *et al.* with the teachings of Grange *et al.* A prima facie case of obviousness has not been established. Appellant therefore respectfully requests that the Board

reverse the Examiner as to the issue of whether Appellants' claimed invention is unpatentable over Lindmo *et al.* in view of Grange *et al.* under 35 U.S.C. §103(a). Since the remainder of the rejections under 35 U.S.C. §103(a) require the combination of Lindmo *et al.* and Grange *et al.*, they will be obviated by the withdrawal of the rejections based on these two references only.

Respectfully submitted,



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APPENDIX A

CLAIMS:

1. A reagent for an agglutination assay for determining an analyte in a sample, said reagent comprising a mixture of microparticles, said mixture comprising first microparticles having a mean diameter from 30 to 600 nm and a refractive index, wherein said first microparticles are coated with a first binding partner for said analyte, and second microparticles having a mean diameter from 30 to 600 nm and a refractive index, wherein said second microparticles are coated with a second binding partner for said analyte, said first microparticles having stronger light scattering properties than said second microparticles, and said first binding partner having a higher reactivity for said analyte than said second binding partner, said microparticles being capable of causing light scattering at wavelengths between 300 and 1200 nm.

2. The reagent of claim 1, wherein said mean diameter of said first microparticles is greater than said mean diameter of said second microparticles.

3. The reagent of claim 2, wherein said refractive index of said first microparticles is greater than said refractive index of said second microparticles.

4. The reagent of claim 3, wherein a ratio of the mean diameter of said first microparticles to the mean diameter of said second microparticles ranges from about 1.5 to about 4.0.

5. (Canceled)

6. The reagent of claim 1, wherein said first microparticles and said second microparticles have a concentration ratio in said mixture of from about 0.01 to about 5.0.

7. (Canceled)

8. (Canceled)

9. The reagent of claim 1, wherein said analyte is a nucleic acid and said first and second binding partners are oligonucleotide capture probes.

10. The reagent of claim 1, wherein said analyte is antigenic and said first and second binding partners are monoclonal antibodies or fragments thereof.

11. (Canceled)

12. (Canceled)

13. (Canceled)

14. (Canceled)

15. (Canceled)

16. (Canceled)

17. (Canceled)

18. (Canceled)

19. (Canceled)

20. The reagent of claim 1, wherein said first and second microparticles have a composition selected from the group consisting of selenium, carbon, gold, a nitride of carbon, a nitride of silicium, a nitride of germanium, an oxide of iron, an oxide of titanium, an oxide of silicium, an epoxy resin, polyvinyl chloride, polyvinylidene chloride, polyalpha-naphthylmethacrylate, polvinylnaphthalene, polystyrene and a copolymer thereof.

21. (Canceled)

22. The reagent of claim 1, wherein the analyte is C-reactive protein and the first and second binding partners recognize different epitopes of C-reactive protein.

23. The reagent of claim 1, wherein the analyte is prostate specific antigen and the first and second binding partners recognize different epitopes of prostate specific antigen.